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Editorial Comment

Enhancing Thrombolytic Efficacy By Means of "Front-Loaded" Administration of Tissue Plasminogen Activator*

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Unresolved problems with thrombolytic therapy. During the last 6 years, coronary thrombolysis has rapidly become established as a major advance in the treatment of selected patients with acute myocardial infarction. When successful, thrombolysis causes reperfusion of occluded coronary arteries, salvages ischemic myocardium, prevents left ventricular dysfunction and enhances both early and late survival. However, unresolved problems with this therapy persist (1). First, coronary arteriography carried out immediately after intravenous infusion of the thrombolytic agent demonstrates that reperfusion of the infarct-related artery does not occur uniformly. After the intravenous administration of recombinant tissue-type plasminogen activator (rt-PA), perhaps the most effective thrombolytic agent now available, approximately 25% of patients exhibit persistent coronary occlusion (2). Other limitations of thrombolytic therapy include a modest incidence of reocclusion and bleeding complications. Furthermore, there is debate concerning the identification of appropriate patients for treatment, especially patients with ST segment depression, as well as patients presenting >6 h after the onset of symptoms (1). Other unresolved problems include selection of the appropriate adjuvant therapy to prevent reocclusion and to minimize reperfusion injury.

The present study. The lack of therapeutic efficacy is an especially vexing problem. Not unexpectedly, mortality is particularly high in patients whose occluded coronary artery fails to open (3). This potentially serious limitation of efficacy appears to have been addressed successfully by Neuhaus et al. (4) in a simple and straightforward manner. These investigators "front loaded" the dose, commencing with a bolus of 15 mg, followed by 50 mg in the next 30 min and the remaining 35 mg in the following 60 min. Coronary patency, defined as Thrombolysis in Myocardial Infarction (TIMI) class 2 or 3 (5), was observed in 90.5% of 74 patients studied arteriographically at 90 min. To my knowledge, this is the highest patency rate following the intravenous administration of any thrombolytic agent thus far reported, and it is apparently superior to the approximately 75% patency rate previously reported with the standard rt-PA regimen (60 mg for 1 h with a 6 to 10 mg bolus dose and 20 mg during each of the subsequent 2 h). This salutary result was not associated with an excessive rate of reocclusion (10.5%) or bleeding.

Although these observations are impressive and encouraging, before recommending the widespread adoption of the "Neuhaus regimen," it is desirable to carry out a controlled randomized trial comparing it with the standard regimen. It might be even more appropriate to compare the "front-loaded" Neuhaus regimen with the standard regimen using weight-adjusted doses because the latter not only is more logical, but also may have some advantages over the fixed 100 mg dose (6). Such a comparison is essential to evaluate this new regimen because of the well known problems associated with the use of historical controls and because, in most of the earlier studies with rt-PA, angiographic patency was assessed at approximately 90 min after the onset of therapy, before the infusion of the full dose, thereby probably underestimating thrombolytic efficacy. However, if the results of an appropriately controlled comparison confirm the superiority of the "Neuhaus regimen," then it (or a weight-adjusted modification) should be substituted for the standard approach.

Implications. Currently there is considerable interest in the use of genetically engineered mutants of t-PA (7) whose principal advantage over native t-PA appears to be a longer half-life measured in hours instead of minutes. These mutants can be administered as a bolus rather than an infusion, and such a bolus can rapidly achieve a high concentration of circulating drug. If, as is strongly suggested by the data of Neuhaus et al. (4), rapidly achieving a high concentration of rt-PA enhances thrombolysis, then it is possible that this advantage will also be attained with the bolus injection of appropriate mutants that may possess the additional desirable feature of providing a sustained high plasma concentration, thus avoiding the need for more than one injection.

Although thrombolytic therapy is now well established treatment for many patients with acute myocardial infarction, considerable "fine tuning" is necessary to enhance its efficacy and broaden its applicability. The study by Neuhaus et al. (4) may well prove to be a useful contribution of this nature.

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